



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 March 2012

The draft opinion adopted by Transparency Committee on January 18th, 2012 has been discussed during a hearing on March 14th, 2012.

ESBRIET 267 mg, hard capsules

B/63 (CIP code: 416 883-1)

B/252 (CIP code: 416 884-8)

Applicant: INTERMUNE FRANCE

pirfenidone

ATC code: L04AX05 (Immunosuppressants)

List I

Medicine for hospital prescription only restricted to pulmonologists.
Medicine requiring special monitoring during treatment.

Orphan medicinal product (date of designation): 16 November 2004

Date of Marketing Authorisation (centralised procedure): 28 February 2011

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

pirfenidone

1.2. Therapeutic indication

"ESBRIET is indicated in adults for the treatment of mild to moderate Idiopathic Pulmonary Fibrosis (IPF)."

1.3. Dosage

Treatment with ESBRIET should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of IPF.

"Adults

Upon initiating treatment, the dose should be titrated to the recommended daily dose of nine capsules per day over a 14-day period, the dose being progressively increased up to the recommended dose as follows:

- days 1 to 7: one 267 mg capsule, three times a day (801 mg/day)
- days 8 to 14: two capsules, three times a day (1602 mg/day)
- day 15 onwards: three capsules, three times a day (2403 mg/day)

The recommended daily dose for patients with IPF is three 267 mg capsules three times a day with food, or a total of 2403 mg/day.

Doses above 2403 mg/day are not recommended for any patient, regardless of their health.

Patients who miss 14 consecutive days or more of treatment should re-initiate therapy by undergoing the initial 2-week titration regimen up to the recommended daily dose.

For treatment interruption of less than 14 consecutive days, the dose can be resumed at the previous recommended daily dose without titration.

Dose adjustments and other considerations for safe use:

Gastrointestinal events: In patients who experience intolerance to therapy due to gastrointestinal side effects, patients should be reminded to take the medicinal product with food. If symptoms persist, the dose may be reduced to 1-2 capsules (267 mg – 534 mg) 2-3 times per day with food with re-escalation to the recommended daily dose as tolerated. If symptoms continue, patients may be instructed to interrupt treatment for 1 to 2 weeks to allow symptoms to resolve.

Photosensitivity reaction or rash:

Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded of the instruction to use a sun-block daily and to avoid sun exposure (see section 4.4 of the SPC). The dose of ESBRIET may be reduced to 3 capsules per day (1 capsule three times a day). If the rash persists after 7 days, treatment should be discontinued for 15 days, with re-escalation to the recommended daily dose in the same manner as the dose escalation period.

Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice immediately (see section 4.4 of the SPC). Once the rash has resolved, treatment may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the physician.

Hepatic function: In the event of significant elevation of alanine and/or aspartate aminotransferases (ALT/ AST) with or without bilirubin elevation, the dose of ESBRIET should be adjusted or treatment discontinued according to the guidelines listed in section 4.4 of the SPC.

Special populations

Elderly:

No dose adjustment is necessary in patients 65 years and older (see section 5.2 of the SPC).

Hepatic impairment:

No dose adjustment is necessary in patients with mild to moderate hepatic impairment (i.e. Child-Pugh Class A and B). However, since plasma levels of pirfenidone may be increased in some individuals with mild to moderate hepatic impairment, caution should be used with ESBRIET treatment in this population (see section 5.2 of the SPC). The safety of treatment should be monitored closely in patients especially if they are concomitantly taking a known CYP1A2 inhibitor (see sections 4.5 and 5.2 of the SPC).

ESBRIET has not been studied in patients with severe hepatic impairment or end stage liver disease. Consequently, it should not be used in patients with these conditions (see sections 4.3, 4.4 and 5.2 of the SPC).

It is recommended to monitor liver function during treatment, and dose adjustments may be necessary in the event of elevations (see sections 4.4 and 5.2 of the SPC).

Renal impairment:

No dose adjustment is necessary in patients with mild to moderate renal impairment. ESBRIET therapy should not be used in patients with severe renal impairment (CrCl < 30 ml/min) or end stage renal disease requiring dialysis (see sections 4.3 and 5.2 of the SPC).

Paediatric population:

There is no relevant use of ESBRIET in the paediatric population in the treatment of idiopathic pulmonary fibrosis.

Method of administration

The capsule is to be swallowed whole with water and taken with food to reduce the possibility of nausea and dizziness (see sections 4.8 and 5.2)."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

L: Antineoplastic and immunomodulating agents
L04: Immunomodulators / Stimulants
L04A: Immunosuppressants
L04AX: Other immunosuppressants
L04AX05: pirfenidone

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

There are no other medicinal products with a marketing authorisation for the treatment of idiopathic pulmonary fibrosis.

In theory, acetylcysteine may be used as monotherapy off label use.¹

¹ Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788-824

3 ANALYSIS OF AVAILABLE DATA

In support of its request, the pharmaceutical company has provided the following data:

- randomised, double blind phase III studies versus placebo, PIPF-004 and PIPF-006; as well as their pooled analysis
- randomised, double blind phase III study versus placebo, SP3, comparing two doses of pirfenidone versus placebo;
- a pooled analysis of these three studies;
- a Cochrane meta-analysis, comparing non-steroidal active substances to a placebo or a corticosteroid;
- the open-label study RECAP (PIPF-012), monitoring the long-term tolerance of the product, including patients who had completed studies PIPF-004 and PIPF-006.

3.1 Efficacy

3.1.1 Studies PIPF-004 and PIPF-006

Aims and methods

The aim of studies PIPF-004 and PIPF-006 was to evaluate the efficacy and tolerance of pirfenidone (2,403 mg/day) in patients with idiopathic pulmonary fibrosis (IPF). Both studies had the same experimental methods, with the exception of there being a third group of patients treated with an intermediate dose of pirfenidone (1,197 mg/day) in the PIPF-004 study, to determine the dose/response relationship. No statistical analysis was included in the protocol for this arm and the dose was outside of the scope of the marketing authorisation, therefore the results will not be described.

A prespecified pooled analysis was carried out for studies PIPF-004 and PIPF-006.

Methods: controlled, randomised, double blind phase III trials, versus placebo, with a minimum duration of 72 weeks.

The studies included:

- a 28 day wash-out period (during this period, patients had to stop taking any medication such as cytotoxics, immunosuppressants, immunomodulators, endothelin receptor antagonists, treatments for IPF or an experimental therapy),
- and a minimum 72 week period of treatment with pirfenidone, following the dose regimen stated in the SPC.

Main inclusion criteria:

Patients aged from 40 to 80 years with IPF diagnosed within the last 48 months, with a predictive forced vital capacity² pFVC \geq 50% of the theoretical value and a DLCO³ \geq 35% of the predicted value and without improvement in the level of severity of IPF during the year prior to inclusion in these studies.

There is no consensus on the definition of severity for IPF.

Primary efficacy endpoint: change from baseline to week 72 in the predictive forced vital capacity (FVC, % of the predicted value).

Main secondary endpoints (evaluated at 72nd week of treatment):

- Categorical assessment of absolute change from baseline to week 72 in absolute pFVC value (predictive forced vital capacity, % of the predicted value)⁴
- progression-free survival, defined as time to the first occurrence of either of the following (as compared to the patient's baseline): 10% absolute decline in percent predicted FVC⁵, or 15% absolute decline in percent predicted Hgb-corrected DLCO⁶ or death
- change from baseline to week 72 in the distance covered during the 6-minute walking test (6MWT)
- change from baseline to week 72 in oxygen saturation, measured through pulse oximetry during the 6-minute walking test
- change from baseline to week 72 in the percent predicted Hgb-corrected DLCO
- change from baseline to week 72 in dyspnoea
- Time to worsening of IPF, a composite endpoint defined as: time to acute IPF exacerbation, IPF-related death, lung transplantation or respiratory hospitalization.

Main exploratory endpoints: overall survival, quality of life

² FVC is a measurement of forced expiration. The patient is in a seated or standing position. They then breathe in as deeply as possible and forcibly exhale all the air from their lungs into a spirometer. The results from the spirometer are compared with theoretical or predicted values, which are calculated based on the age, sex, height and ethnic origin of the patient. The FVC% expresses the percentage of the FVC compared with this predicted value.

³ Carbon monoxide diffusing capacity

⁴ This change is measured using the following criteria:

- severe decline: decline of pFVC \geq 20% or death or lung transplant
- moderate decline: decline of pFVC $<$ 20% but \geq 10%
- mild decline: decline of pFVC $<$ 10% but \geq 0%
- mild improvement: improvement of pFVC $>$ 0% but $<$ 10%
- moderate improvement: improvement of pFVC \geq 10%

⁵ variation evaluated between 2 consecutive visits performed at least 6 weeks apart

Efficacy results

➤ Characteristics of patients included

In study PIPF-004, 435 patients were included and in study PIPF-006, there were 344 patients.

Table 1:

Criteria	Study PIPF-004		Study PIPF-006	
	Pirfenidone 2403 mg/day N = 174	Placebo N = 174	Pirfenidone 2403 mg/day N = 171	Placebo N = 173
age				
mean ± SD	65.7 ± 8.15	66.3 ± 7.53	66.8 ± 7.90	67.0 ± 7.80
≥ 65 years (n)	99	101	101	112
pFVC (%)				
n	174	174	171	173
mean ± SD	74.5 ± 14.47	76.2 ± 15.51	74.9 ± 13.15	73.1 ± 14.21
DLCO (%)				
n	174	172	171	173
mean ± SD	46.4 ± 9.49	46.1 ± 10.24	47.8 ± 9.82	47.4 ± 9.15
6MWT distance (m)				
n	170	170	169	168
mean ± SD	411.1 ± 91.87	410.0 ± 90.93	378.0 ± 82.24	399.1 ± 89.74
Oxygen use, n (%)				
yes	29 (16.7%)	25 (14.4%)	48 (28.1%)	49 (28.3%)
no	145 (83.3%)	149 (85.6%)	123 (71.9%)	124 (71.7%)
Time between diagnosis of IPF and randomisation (years)				
n	174	174	171	172
mean ± SD	1.3 ± 0.96	1.4 ± 1.12	1.2 ± 1.09	1.1 ± 0.99

➤ Results for the primary efficacy endpoint

At week 72, in study PIPF-004, the absolute mean decline in pFVC was 8.0% in the pirfenidone group (n=174) and 12.4% in the placebo group (n=174), ie a difference of 4.4% (95% CI [0.7; 9.1], p = 0.001).

In study PIPF-006, no difference between the groups was observed.

In the pooled analysis of studies PIPF-004 and PIPF-006, the absolute mean decline in pFVC was 8.5% in the pirfenidone group (n=345) and 11.0% in the placebo group (n=347), ie a difference of 2.5% (CI not available, p = 0.005).

➤ Results for the secondary endpoints

- *Categorical assessment of absolute change from baseline to week 72 of pFVC value*
In studies PIPF-004, the following was observed:
 - a mild to moderate improvement in pFVC for 42 patients in the pirfenidone group (n=174) and 24 patients in the placebo group (n=174), with 2 moderate improvements in the pirfenidone group and 0 in the placebo group, p < 0.0001;
 - a mild to moderate decline in pFVC for 118 patients in the pirfenidone group (n=174) and 123 patients in the placebo group (n=174), p < 0.001;
 - a severe decline in pFVC for 14 patients in the pirfenidone group (n=174) and 27 patients in the placebo group (n=174).

In study PIPF-006, no difference between the two groups was observed for this endpoint.

- *Progression-free survival:*
In study PIPF-004, the relative risk of progression or death was 0.64 (95% CI, [0.44; 0.95], $p = 0.023$).
In study PIPF-006, no difference between the two groups was observed for this endpoint.
- *Distance covered during the 6-minute walk test (6MWT)*
In study PIPF-004, no difference was observed.
In study PIPF-006, a reduction was observed in the distance covered during the 6-minute walk test of 45.1 m in the pirfenidone group ($n=171$) and 76.9 m in the placebo group ($n=173$), or a difference of 31.8 m (CI not available, $p < 0.001$).
- *Change in oxygen saturation during the 6-minute walk test, change in DLCO, assessment of dyspnoea, delay in worsening of IPF:*
No differences were observed for these endpoints.

3.1.2 **Study SP3**

This study is described for information purposes only, as it was included in the pooled analysis of trials carried out by the pharmaceutical company and in the Cochrane meta-analysis described in this document. However, there are issues with the transferability of data from this trial as it was carried out in Japan and has an inadequate method (amendment to efficacy endpoint, non-validated patient selection criteria, etc.).

Aims and methods

Primary aim: Evaluate the efficacy and tolerance of pirfenidone at a dose of 1,800 mg/day (comparable to the dose of 2,403 mg/day for the American and European patients in studies PIPF-004 and PIPF-006 on a normalised weighted basis) for Japanese patients with idiopathic pulmonary fibrosis (IPF). The secondary objective of this trial was to evaluate the efficacy and tolerance of a reduced dose of pirfenidone (1,200 mg/day) compared with a dose of 1,800 mg/day and with placebo in patients with IPF. As this lower dose (1,200 mg/day) was not part of the marketing authorisation, the corresponding results are not presented.

Methods: Randomised, double blind phase III study, versus placebo carried out on 275 patients over a 52 week period. To be included in the study, the patients (aged between 20 and 75 years) had to have IPF diagnosed both clinically and radiologically.

Primary efficacy endpoint: change in vital capacity from baseline to Week 52.

Main secondary endpoints (evaluated at Week 52):

- progression-free survival, defined as the time to the first occurrence of death or a reduction of at least 10% in vital capacity evaluated
- change in SpO₂ during the 6-minute walk test, compared with the value at baseline.

Efficacy results

➤ Characteristics of patients included

In total, 275 patients were randomised: 110 in the pirfenidone 1,800 mg/day group and 109 in the placebo group.⁶ The mean age of patients was 65.4 years in the pirfenidone

⁶ 56 in the pirfenidone 1,200 mg/day group

1,800 mg/day group and 64.7 years in the placebo group. The mean vital capacity of patients was 2,401 ml in the pirfenidone 1,800 mg/day group and 2,472 ml in the placebo group.

➤ Results for the primary efficacy endpoint

At Week 52, the vital capacity had decreased by 90 ± 20 ml in the pirfenidone group and by 160 ± 20 ml in the placebo group (difference of 70 ml, $p=0.042$).

➤ Secondary endpoint results:

The relative risk of progression or death was 0.45 (95% CI, [0.11; 0.79], $p = 0.028$).

No difference was observed with regard to changes in SpO₂ during the 6-minute walk test.

3.1.3 Pooled analysis for studies PIPF-004, PIPF-006 and SP3

The aim of this analysis, which combined results from studies PIPF-004 and 006 and SP3, carried out by the pharmaceutical company, was to evaluate the effect of pirfenidone in the reduction of pFVC or VC based on the trials and in terms of progression-free survival.

The efficacy endpoints were different depending on the studies with no test for heterogeneity being carried out. These results should therefore be interpreted with caution.

Results, presented for information only:

- change in pFVC or VC: RR = 0.24 (95% CI, [0.10; 0.37], $p = 0.0009$).

- progression-free survival: RR = 0.71 (95% CI, [0.57; 0.89], $p = 0.0026$).

3.1.4 Cochrane meta-analysis⁷

The aim of this meta-analysis was to evaluate the efficacy of treatment, other than corticosteroid therapy, for patients with IPF.

The 15 studies included in this meta-analysis were randomised studies, comparing non-steroid agents to a placebo or a corticosteroid.

The primary efficacy endpoints were the overall survival and progression-free survival.

Exhaustive research of data was carried out. Heterogeneity tests did not give significant results.

Among the treatments evaluated, the authors were interested in interferon γ -1- β and pirfenidone, as these were molecules that had more than one clinical trial available.⁸ No difference was observed between interferon and placebo when it came to overall survival.

For pirfenidone, evaluated versus placebo, the relative risk of progression-free survival was 0.70 (95% CI [0.56; 0.88], $p = 0.002$).

The authors of the meta-analysis considered that for the other treatments (azathioprine, cyclophosphamide, colchicine, etanercept and imatinib), evaluated in a single clinical trial, there was insufficient data to draw any conclusions about their clinical use and that other trials would be required.

⁷ Spagnolo P, Del Giovane C, Luppi F, et al. Non-steroid agents for idiopathic pulmonary fibrosis. Cochrane Database Syst Rev. 2010 Sep 8; (9): CD003134

⁸Four studies on pirfenidone and two studies on interferon γ -1- β .

3.2 Adverse effects

3.2.1 Studies PIPF-004 and PIPF-006

Adverse events considered as being linked to treatment were observed in 314/345 patients in the pirfenidone 2,403 mg/day group and 240/347 patients in the placebo group.

The most commonly observed adverse events were: nausea (36.2% in the pirfenidone group versus 17.3% in the placebo group), diarrhoea (28.7% versus 19.3%), dyspepsia (19.1% versus 7.5%); fatigue (30.1% versus 20.5%), headaches (18.8% versus 16.1%) and dizziness (18.3% versus 10.1%); upper respiratory tract infections (30.7% versus 29.4%), anorexia (10.7% versus 3.7%) and a loss of appetite (8.7% versus 2.9%), skin disorders (44.1% versus 17.9%) including photo-sensitivity reactions (12.2% versus 1.7%) and rash (32.2% versus 11.5%).

51 in the pirfenidone group and 30 in the placebo group stopped treatment due to adverse events.

The most common causes of death were IPF and respiratory failure. There were 19 deaths in the pirfenidone group (including 12 due to IPF) and 29 in the placebo group (including 25 due to IPF).

3.2.2 Study SP3

The most commonly observed adverse effects in the pirfenidone 1,800 mg/day group compared with the placebo group were: photo-sensitivity reactions (51.4% versus 22.4%), rhinopharyngitis (49.5% versus 65.4%), anorexia (16.5% versus 2.8%) and stomach discomfort (14.7% versus 11.2%).

42/110 patients in the pirfenidone 1,800 mg/day group and 36/109 patients in the placebo group stopped treatment due to adverse events.

3.2.3 RECAP Study (Study PIPF-012)

The pharmaceutical company provided intermediate results (available up to 27 April 2009) from an open-label study, which is still in progress, with the main objective to collect long-term tolerance data from patients treated with pirfenidone at a dose of 2,403 mg/day and who had completed the PIPF-004 or PIPF-006 studies. Data presented by the pharmaceutical company was for results at 106 weeks.

Patients who received a placebo or pirfenidone at a dose of 1,197 mg/day in the PIPF-004 study were all treated with pirfenidone at a dose of 2,403 mg/day in this study.

In total, 603 patients were included, aged from 42 to 83 years (median age 69 years). Among these patients, 261 had been previously treated with pirfenidone 2,403 mg/day, 274 previously received the placebo and 68 were previously treated with pirfenidone 1,197 mg/day.

The mean treatment duration for this study, at the date when data was submitted, was 29.4 weeks.

Adverse events were reported by 243 patients (93.1%) who were previously treated with pirfenidone 2,403 mg/day, 264 patients (96.4%) who previously received a placebo, and 66 patients (97.1%) who were previously treated with pirfenidone 1,197 mg/day.

The most commonly observed adverse events (>10%) were: nausea (21.2% of patients), upper respiratory tract infections (15.1%), diarrhoea (14.6%), nasopharyngitis (14.3%), headaches (11.4%), dyspepsia (10.8%), cough (10.6%), fatigue (10.6%), bronchitis (10.1%), and dizziness (10.0%).

48 patients stopped treatment due to adverse events.

Adverse events considered as being linked to treatment with pirfenidone, essentially nausea, were reported by 143 patients (54.8%) previously treated with pirfenidone 2,403 mg/day,

197 patients (71.9%) who had previously received a placebo and 39 patients (57.4%) who were previously treated with pirfenidone 1,197 mg/day.

There were 25 deaths reported, including 23 in the 28 days after the first dose of pirfenidone. Among these 23 deaths, 12 were considered as being linked to IPF.

3.2.4 Special warnings and precautions for use (see SPC)

Hepatic function

Elevations in ALT and AST $>3 \times$ upper limit of normal (ULN) have been reported in patients receiving therapy with ESBRIET. Liver function tests (ALT, AST and bilirubin) should be conducted prior to the initiation of treatment with ESBRIET, and subsequently at monthly intervals for the first 6 months and then every 3 months thereafter.

Photosensitivity reaction and rash

Exposure to direct sunlight (including sunlamps) should be avoided or minimised during treatment with ESBRIET. Patients should be instructed to use a sun-block daily, to wear clothing that protects them against sun exposure, and to avoid other medicinal products known to cause photosensitivity. Patients should be instructed to report symptoms of photosensitivity reaction or rash to their physician. Severe photosensitivity reactions are uncommon. Dose adjustments or temporary treatment discontinuation may be necessary in mild to severe cases of photosensitivity reaction or rash.

Dizziness

Dizziness has been reported in patients taking ESBRIET. Therefore, patients should know how they react to this medicinal product before they engage in activities requiring mental alertness or coordination (see section 4.7 of SPC). In clinical studies, most patients who experienced dizziness had a single event, and most events resolved, with a median duration of 22 days. If dizziness does not improve or if it worsens in severity, dose adjustment or even discontinuation of ESBRIET may be warranted.

Weight loss

A loss in weight, in the order of 3 to 4 kg, has been reported in patients taking ESBRIET (see section 4.8 of SPC). Physicians should monitor patients' weight, and when appropriate encourage increased caloric intake if weight loss is considered to be of clinical significance.

3.2.5 Risk management plan (RMP)

A RMP was approved by EMA. This plan primarily establishes the monitoring of certain adverse events as part of normal pharmacovigilance, such as photosensitivity reactions and rash, liver enzymes, dizziness, loss of weight, gastrointestinal disorders, fatigue and interactions with certain medicines.

3.3 Conclusion

Pirfenidone at a dose of 2,403 mg/day, was primarily evaluated after 72 weeks in two randomised, double blind studies (PIPF-004 and PIPF-006) versus placebo, for a total of 779 patients with idiopathic pulmonary fibrosis (IPF)

According to the wording of the marketing authorisation, pirfenidone is indicated for the treatment of "mild to moderate" IPF. The stages of evolution of IPF, as stated in the indication in the marketing authorisation, do not have a clear, precise definition that is recognised unanimously. Therefore, patients with IPF likely to benefit from treatment with pirfenidone need to be defined based on the pulmonary function parameters of patients included in studies PIPF-004 and PIPF-006 and recommended⁹, namely FVC \geq 50% and a DLCO \geq 35%.

The patient characteristics in these two studies were comparable.

At Week 72, in study PIPF-004, the absolute difference between the pirfenidone treatment group and the placebo group for forced vital capacity (in % of the predicted value), a primary efficacy endpoint, was 4.4% (95% CI [0.7; 9.1], $p = 0.001$). In study PIPF-006, there was no difference seen between the two groups for this endpoint.

In the pooled analysis for studies PIPF-004 and PIPF-006, specified in the protocol, this difference was 2.5% (CI not available, $p = 0.005$).

From the morbidity and mortality secondary endpoints:

- no difference was observed for the time to worsening of the IPF endpoint in either of the two studies,
- no difference was observed for the progression-free survival endpoint in study PIPF-006,
- the risk of progression or death was 0.64 (95% CI, [0.44; 0.95], $p = 0.023$) in study PIPF-004.

The efficacy of pirfenidone was determined according to an intermediate endpoint, evaluating the pulmonary function and a marker of the progression of the disease. The difference observed for this endpoint is in favour of pirfenidone compared with placebo; however, this difference is small, of unknown clinical significance and heterogeneous across the two studies. The reason for the difference, which also affects the secondary endpoints, is uncertain.

The clinical benefit for patients with idiopathic pulmonary fibrosis is difficult to determine as clinically relevant criteria (quality of life, overall survival etc.) have only undergone exploratory and non-validated analyses, which is something that the Transparency Committee regrets.

The main adverse events observed were gastrointestinal disorders (nausea, diarrhoea, dyspepsia), skin disorders (photosensitivity and rash) and metabolism and nutrition disorders (anorexia and loss of appetite).

Pirfenidone is not approved by the FDA, who have not taken study SP-3 into account and who have requested that the pharmaceutical company carry out a third study, ASCEND, which is a randomised, double blind phase III study, again versus placebo, with the same intermediate criteria as the primary efficacy endpoint for studies PIPF-004 and PIPF-006, but with a more precise definition of functional diagnostic criteria and a 52 week duration. The results from this study are expected mid 2013.

⁹ Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011 Mar 15;183(6):788-824

3.4 Therapeutic use

The treatment of IPF has been the subject of the recently updated guidelines from the ATS (American Thoracic Society), ERS (European Respiratory Society), JRS (Japanese Respiratory Society) and the LATA (Latin American Thoracic Association).¹⁰

According to these guidelines:

- If IPF is suspected, in the presence of clinical signs (dyspnoea, cough, etc), and in the absence of recognised causes (drug toxicity, environmental exposure, connectivity etc.), diagnosis requires a high resolution CT scan showing an interstitial lung disorder and should be confirmed by a MultiDisciplinary Discussion MDD (including pulmonologists, radiologists, and pathologists). It is at this MDD that treatment should be discussed, based on the stage of IPF.
- Acetylcysteine (off label use), having demonstrated a slowing down in the deterioration in vital capacity, albeit with minimal clinical evidence, may be given to a minority of patients. Treatments not recommended are (absence of acceptable study methods, absence of proof for functional endpoints): corticosteroids as a monotherapy, colchicine, ciclosporine A, interferon γ 1b, bosentan, etanercept, a combination of a corticosteroid and an immunomodulator and triple therapy with a combination of acetylcysteine, prednisone and azathioprine.¹¹
- FVC and DLCO should be evaluated every 3 to 6 months. If IPF worsens (a 10% decrease in FVC and/or 15% in DLCO, criteria associated with an increased risk of death¹²), treatment should be re-evaluated. For patients with worsening and severe forms of the disease, oxygen therapy or a lung transplant are the recommended treatments.

Therapeutic use of ESBRIET

ESBRIET is the first treatment with marketing authorisation to be indicated for mild to moderate IPF. The effect observed with ESBRIET on the decline in lung function for patients with specific functional criteria (FVC \geq 50% and DLCO \geq 35%) is weak. This treatment is therefore only for this specific population of patients with IPF.

¹⁰ Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788-824

¹¹ There was a recent warning issued about this triple therapy combination.

Cottin V, Crestani B, Valeyre D. Alert: triple therapy is no longer a recommended option to treat idiopathic pulmonary fibrosis. This update is a warning and is not a therapeutic recommendation. E-info respiration. 14 February 2012 Available at <http://www.splf.org/e-info-respi/e-info-alerte-23-2-12.html>

¹² During monitoring of this disease, increase in dyspnoea and spreading of fibrosis identified in a CT scan are also associated with an increased mortality risk.

4.1 Actual benefit

Idiopathic pulmonary fibrosis (IPF) is the most common clinical form of idiopathic diffuse interstitial lung disease, representing approximately 60% of all cases. IPF generally occurs between the age of 60 and 70 years, and is rarely seen in those under 50 years of age. The clinical picture combines the progressive onset of shortness of breath, a non-productive cough, and more rarely constitutional symptoms. It is a rare, chronic, fibrotic and inflammatory disorder, with a life-threatening prognosis. It evolves slowly, leading to chronic respiratory failure and death, with a median survival rate of 2 to 3 years⁸, with only 10% of patients surviving for 10 years.

The quantity of effect from pirfenidone is weak, and only involves preserving the respiratory function of patients with specific functional diagnostic criteria. The main adverse events (gastrointestinal, cutaneous, metabolic and nutritional) should be monitored. The efficacy/tolerance ratio for this medicinal product is therefore weak.

This medicinal product is a symptomatic treatment and is intended for patients with a confirmed IPF diagnosis and with a FVC \geq 50% and a DLCO \geq 35%.
There are no other treatments with a marketing authorisation for the treatment of IPF.

Public health benefit:

Idiopathic pulmonary fibrosis is considered as a rare disease (its prevalence is estimated at 16.7/100,000 people in Europe), with a very serious prognosis (median survival rate of 2 to 3 years from diagnosis). Due to the number of people affected the burden of this disease is weak.

The improvement in the management of patients with rare diseases is a public health need set out in the National Rare Diseases Plan 2011-2014.

In view of the available data, pirfenidone (ESBRIET) is expected to have a low impact on morbidity. Its impact on mortality is not clearly demonstrated. ESBRIET does not have an impact on the quality of life of patients treated and ESBRIET and is not expected to have an impact on the healthcare system.

The transferability of results is not assured, especially given the difficulty in monitoring patients and the problems in them complying with treatment protocols. The product needs to be taken three times daily, and frequently leads to general and gastrointestinal problems.

Consequently, ESBRIET is not expected to benefit public health.

The actual benefit of ESBRIET is low, and is only for patients with an IPF diagnosis confirmed both clinically and radiologically, and with the following functional respiratory criteria: **FVC \geq 50% and DLCO \geq 35%**.

4.2 Improvement in actual benefit (IAB)

In view of all the available data, the Transparency Committee considers that ESBRIET provides a minor improvement in actual benefit (IAB IV) for patients evaluated in the trials, namely those with a clinically and radiologically confirmed idiopathic pulmonary fibrosis diagnosis and a **FVC \geq 50% and a DLCO \geq 35%**.

4.3 Target population

The ORPHANET¹³ report, published in May 2011, indicates that the prevalence of idiopathic pulmonary fibrosis is 16.7 cases for every 100,000 inhabitants, which corresponds to a population of 11,000 patients in France.

There is no epidemiological data or bibliographic references allowing the number of patients with IPF to be estimated precisely, based on respiratory functional parameters. However, according to results from the COFI study (a prospective French cohort, involving all 24 university hospital-based respiratory medicine departments), which included 210 patients recently diagnosed with IPF (< 9 months), 70% of patients had a **FVC ≥ 50% and a DLCO ≥ 35% of the predicted value.**

In addition, the target population for ESBRIET, as seen by the Committee (**FVC ≥ 50% and DLCO ≥ 35%**) **would be a maximum of 7,700 patients in France.**

4.4 Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the indication and at the dosages in the Marketing Authorisation and for patients with idiopathic pulmonary fibrosis with a clinically and radiologically confirmed IPF diagnosis and with the following respiratory functional diagnostic criteria: FVC ≥ 50% and DLCO ≥ 35%.

Each diagnosis and idiopathic pulmonary fibrosis treatment should be the subject of a MultiDisciplinary Discussion.

Given the uncertainty regarding the level of effect and the expected clinical benefit of pirfenidone in the treatment of patients with idiopathic pulmonary fibrosis, at the request of the DGS (Directorate-General for Health), the Committee would like data to be provided by the pharmaceutical company on the characteristics of patients treated and the impact on morbidity and mortality in real life practice situations and compared with normal treatments. In the event of the "PASS" register, implemented as part of the Risk Management Plan, not being able to answer the questions raised, a specific study should be carried out. The use of pre-existing cohorts with the disease, especially in France, is encouraged.

4.4.1 Packaging:

The packaging in boxes of 63 capsules is appropriate for the prescription conditions for the 14 day initiation phase.

The packaging in boxes of 252 capsules is appropriate for the prescription conditions after the initiation phase.

4.4.2 Reimbursement rate: 15%

4.4.3 The Committee recommends that this proprietary medicinal product is granted exception drug status.

¹³ Orphanet report series. Rare disease collection. May 2011 – Number 1. Available at http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.